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EDITORIAL

Resection margins in pancreatic cancer: are we entering a new era?

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Controversy regarding various aspects of microscopic margin involvement (R1) in pancreatic cancer has resulted in conflicting published data on the R1 rate and the prognostic significance of margin involvement. In recent years, several studies indicated that when using a standardized pathology protocol based on axial specimen slicing and reporting margin involvement if tumour cells are present within 1 mm from the margin, the R1 rate increases significantly, from a traditional value around 20% to more than 70%.[1–4] However, these studies suffer from being retrospective and based on a small series and/or a long study period during which patient selection and post-operative treatment were not uniform. In this issue of *HPB*, Delpero *et al.*[5] present a multicentre study, which prospectively analysed resection margin involvement in pancreatoduodenectomy specimens (PDEs) for pancreatic ductal adenocarcinoma. The prospective multicentre study design is a novelty in this area of clinical research, and the study also distinguishes itself favourably from previous analyses by its fairly large series ($n = 150$), the short study period (2 years), and the use of a standardized pathology protocol based on axial slicing and examination of five distinct margins [posterior, facing the superior mesenteric vein (SMV) and artery (SMA), pancreatic neck, and common bile duct]. Furthermore, the study is the first to apply the quality pathology protocol to PDEs with portal vein (PV)/SMV resection and to assess in a prospective manner the R1 rate based on a range of clearances (0–2 mm). The latter addresses the current controversy regarding the adequate clearance on which to base the R1 definition in pancreatic cancer.

The main observation of the study is a high R1 rate (61%–71%) when using the standardized quality pathology protocol and reporting margin involvement based on a clearance of < 1–2 mm. In contrast, when applying a 0-mm clearance definition, the R1 rate in the same PDE series is only 23%. These results confirm those of previous studies[6,7] and, given the unique methodological strength of this study, leave little doubt that differences in the R1 rate between previously published studies are a result of divergence in pathology examination, not quality of surgery. This leads to the sobering realization that a substantial number of data in the literature are difficult to interpret or compare. At the same time, the study is encouraging because it ushers us into a new era, in which meticulous and standardized pathology examination is a recognized prerequisite for obtaining robust and reproducible data. It highlights the responsibility, first and foremost of the profession of pathology, to ensure that high-quality pathology examination of pancreatic resection specimens becomes established practice.

The study by Delpero *et al.* makes several additional important observations. First, the authors report that the SMV-facing margin (SMVm) is the most frequent site of margin involvement. What might be the reason for this? Considering the microanatomy of PDEs, the finding is not surprising, because the peripancreatic soft tissue layer is minimal or completely absent between the pancreatic parenchyma and the overlying SMV-groove, such that a 'buffer zone' between the infiltrating tumour and the specimen surface is lacking. There are, however, probably other explanations that are related to the composition of the study series. Twenty-four percent of the PDEs included a PV/SMV resection, indicating that nearly a fourth of the tumours had caused significant tethering of the vein owing to infiltration around and possibly into the vessel wall. It seems obvious that in these cases the SMVm – and not another margin – is involved. A similar selection bias results from the inclusion of patients, who had undergone neoadjuvant treatment (19% of the series), mostly for vascular engagement as the authors explain. Hence, the fact that in 43% of the series, the tumour was located in the left-lateral aspect of the pancreatic head and of a considerable size, such that neoadjuvant treatment and/or PV/SMV were required, is likely to have influenced the site of margin involvement.

The SMA-facing margin (SMAm) was found to be the second most frequent site of R1. Considering the above and the fact that both margins are neighbouring and of a smaller width than the average pancreatic cancer, this finding is to be expected. However, the authors' conclusion that the vascular margin, i.e. the combined SMVm and SMAm, is the most important, needs to be met with caution. Both margins may be the most frequently involved, especially in series including patients with venous resection or

neoadjuvant treatment, but whether they are the most important in terms of outcome remains to be seen. Results from previous studies have been conflicting,[4,8] and there is no obvious reason why involvement of one margin should be of greater prognostic importance than that of another, except possibly for the fact that the density of lymphovascular channels and peripheral nerves differs between the various areas of peripancreatic soft tissue, and is highest in the SMA-facing region. The question of the prognostic significance of the site of margin involvement may be more of an academic interest, because if a pancreatoduodenectomy is performed according to current standards, there is no scope for extended resection at the circumferential margins. Furthermore, as margin involvement is rarely the sole adverse factor, the site of margin involvement – even if found to be prognostically significant – is unlikely to influence post-operative treatment.

Heterogeneity of the case series is the main limitation of this study. Inclusion of PDEs after neoadjuvant treatment not only skews the distribution of the tumour site and size, it also raises concerns over the accuracy of margin involvement, because treatment-induced alteration of the tumour growth pattern challenges the rationale on which R1 assessment is currently based.[9,10] Inclusion of invasive intraductal papillary mucinous neoplasia with an overrepresentation of early cancers, of pT4 tumours, and of cancers with features that are highly unusual for conventional ductal adenocarcinoma (e.g. metastasis to 50 lymph nodes) further compounds the issue.

As this is the first prospective multicentre study on resection margins in pancreatic cancer, the interested reader may have questions as to how the study was conducted. How many cases were performed in the various centres? How concurrent were the results? Was there a dedicated study pathologist in each centre, or were specimens reported by various staff members, including trainees? How extensively were the resection margins sampled? Was central pathology review undertaken and did this include review of macroscopic pictures to ascertain the cancer origin?[1,11] How were the venous resections examined, and what were the findings regarding the depth of invasion? Although these questions pertain to critical issues in pathology quality assurance, they are not addressed. Therefore, it is with great anticipation that we look forward to the announced future publication of observations from this study, because much can be expected to be learnt from it, not only in terms of margin involvement and its clinical implications, but also regarding multicentre study design and pathology quality control. After decades of confusion, it seems we are now finally entering an era of controlled and systematic study.

Conflicts of interest

None declared.

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